REMARKS/ARGUMENTS

Claims 1-2, 5, 8, 10-12, 24, and 27 are active. Claims 6, 7, 9, and 13 and 19-23 have been withdrawn from consideration. Only minor edits have been made to claims 1 and 27. In view of the nature of these amendments the Applicants respectfully request entry of this Amendment to place this application in condition for allowance or in better condition for appeal. The proposed amendments do not raise new issues or necessitate a new search by the Examiner, since the amendment is based on elements earlier claimed or inherent in the previously examined claims. Entry of this Amendment would also permit the Applicants to respond to new arguments raised in the final rejection.

Restriction/Election

The Applicants previously elected with traverse Group I as directed to a process of *in vitro* detection of resistant cancer cells to oxaliplatin treatment and to the following species: colorectal cancer, Bax, and TNF. The Requirement has now been made FINAL. The Applicants respectfully request rejoinder and examination of any non-elected species upon an indication of allowability for a generic claim reading on the elected species. Rejoinder of claims in the non-elected groups which depend from or otherwise include all the limitation of an allowed elected claim is also respectfully requested, MPEP 821.04.

Rejections—35 U.S.C. §103

Claims 1, 2, 5, 8, 10, 12, 24 and 27 were rejected under 35 U.S.C. §103(a) as being unpatentable over Maurer, et al., Dig. Dis. Sci. 43:2641, in view of Macpherson, et al., PAACR Ann. Mtg. 43:407 and Chao, et al., J. Exp. Med. 182:821. This rejection cannot be sustained because none of these references suggests that a reduced level of expression of Bax

gene alone correlates with enhanced resistance to oxaliplatin. Thus, the prior art does not disclose or suggest all the elements of the invention.

The Applicants respectfully traverse that the Office has established a *prima facie* case for obviousness. As noted above, the prior art does not disclose or suggest all the elements of the invention. Moreover, the OA does not clearly articulate reasons why the invention would have been obvious to one of ordinary skill in the art at the time of invention.

Maurer did not disclose all the method steps of the present invention, specifically the comparisons between gene expression of pro-apoptotic Bax and/or Bak proteins in cancer cells and in control cells not resistant to oxaliplatin.

The secondary references Macpherson and Chao do not concern detecting the differences between Bax and Bgl expression in tumor and control cells and fail to disclose these elements of the invention as well. Neither of these documents suggests that oxaliplatin resistance correlates with Bax gene expression alone.

Macpherson discloses that the down regulation of Bcl-xl (knock-out mediated by prior antisense) enhances the apoptotic response to oxaliplatin and consequently enhances oxaliplatin cytotoxicity. However, this document did not suggest comparing the level of expression of the gene encoding Bcl-xl in tumor and control cells to determine the degree of oxaliplatin resistance.

Chao is unconcerned with comparing Bax and Bcl expression between cancer and control cells since this document focuses on the parameter of **heterodimerization** of Bcl-2 or of Bax as evident from the citations below:

> This includes Bax, which heterodimerizes with Bcl-2 and **counters** its activity. The **ratio of Bcl-2/Bax** can determine whether a given cell will execute or ignore an apoptotic stimulus (7). (emphasis added, page 821, 1st column).

> Given the existence of one regulatory **pair**, Bcl-2 **and** Bax, that an important question arises as to the rationale for further family members. (emphasis added; page 821, 2nd column).

> . . .in thymocytes from normal control mice, only 30% of Bax is heterodimerized with Bd-xL (Fig. 8A, upper panel), while the supernatant of that immunodepletion reveals that 70% of Bax is unbound (Fig. 8A, lower panel). In contrast, in the presence of the Bcl-xL transgene, a substantial portion of Bax (77%) is heterodimerized with Bcl-xL, while only 23% of Bax is unbound (Fig. 8B). The **heterodimerization of >50% of Bax with either Bcl-2 or Bcl-xL resulted in repression of cell death** in a cell line system (20). (emphasis added; page 825, 2nd column to page 821, 1st column).

Chao only suggests the importance the parameter heterodimerization of Bcl-2 or of Bax, and so the importance of **the ratio of the pair** Bcl-2/Bax compared to the unbound Bcl-2 or Bax to promote or to repress apoptosis in cell. In view of Chao, the person of ordinary skill would have used **the ratio of the pair** Bcl-2/Bax compared to the unbound Bax than the level of Bax expression **alone** as oxaliplatin resistance marker in cancer cell.

Chao only teaches that the inhibition of Bax by heterodimerization with Bcl-xl is associated with an enhanced resistance to oxaliplatin and is silent about whether Bax gene expression alone correlates with resistance. For example, if the level of expression of Bax is high and the level of expression of Bcl-xl is also high, all the Bax proteins will be heterodimerized and thus inhibited—thus, no decreased oxaliplatin resistance despite the high level of Bax expression. Chao is silent about the correlation of Bax expression alone with oxaliplatin resistance.

If the level of expression of Bax is weak and Bcl-xl level experssion weaker, then it will remain free Bax (not heterodimerized with Bcl-xl. Chao, page 827, 2nd col. comments on the importance of the pari association betrween Bax and Bcl0-xl "in normal thymocytes, only a minority of Bax (30%) was heterodimerized with the **modest** levels of Bcl-xl". Therefore, a weak level of expression of Bax is not necessarily correlated with an enhanced resistance to oxaliplatin.

On the other hand, the present claims require the correlation of a reduced expression of a "marker gene expressing the pro-apoptotic Bax and/or Bak protein(s)".

None of the cited documents suggests that in cancer cells, the level of Bax (or Bak) **taken alone** is indicative of oxaliplatin resistance; or as required by claim 1 "wherein reduced expression of said effector or marker gene in said cancer cell compared to said control cell indicates that said cancer cell is resistant to oxaliplatin". Therefore, this rejection cannot be sustained.

Rejections—35 U.S.C. §103

Claims 1, 2, 5, 8, 10-12, 24 and 27 were rejected under 35 U.S.C. §103(a) as being unpatentable over Maurer, et al., Dig. Dis. Sci. 43:2641, in view of Macpherson, et al., PAACR Ann. Mtg. 43:407 and Chao, et al., J. Exp. Med. 182:821, and further in view of Aggarwal, et al., J. Immunol. 160:1627. The four primary references have been discussed above and do not disclose or suggest the invention.

Aggarwal was applied as teaching a quantitative PCR method, but does not remedy the deficiencies in the other applied references. Aggarwal is not concerned with oxaliplatin resistance. Therefore, this rejection cannot be sustained.

Conclusion

This application presents allowable subject matter and the Examiner is respectfully requested to pass it to issue. The Examiner is kindly invited to contact the undersigned should a further discussion of the issues or claims be helpful.

Respectfully submitted,

OBLON, SPIVAK, McCLELLAND,
MAIER & NEUSTADT, P.C.
Norman F. Oblon

Thomas M. Cunningham
Registration No. 45,394

Customer Number
22850

Tel: (703) 413-3000
Fax: (703) 413 -2220
(OSMMN 03/06)